PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CZ2004/000050	24.08.2004	26.08.2003

International Patent Classification (IPC) or both national classification and IPC
C07D491/22

Applicant
PLIVA-LACHEMA A.S.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich	Deutsch, W

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CZ2004/000050

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

V

Reference is made to the following documents:

D1: SAWADA, SEIGO ET AL.: "Synthesis and antitumor activity of 20(S)-campothecin derivatives: carbamate-linked, water soluble derivatives of 7-ethyl-10-hydroxycamptothecin" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 39, no. 6, 1991, pages 1446-1454, XP002306175

D2: US-B-6 235 9071 (HENEGAR KEVIN E ET AL) 22 May 2001 (2001-05-22)

D3: US-A-4 604 463 (SUGINO EIICHI ET AL) 5 August 1986 (1986-08-05)

D4: WO 96/31513 A (UPJOHN CO ; HENEGAR KEVIN E (US); SIH JOHN C (US)) 10 October 1996 (1996-10-10)

Novelty

The compounds of the present application differ from those disclosed in D1 - D4 through the use of dimethylamino pyridine.

Inventive Step

The closest prior art considered to be D1, D2 (see column 23) or D3 (see example 4c).

The only difference between the process of the present claims and those of D1-D3 is the use dimethylaminopyridine for the reaction of the compounds of formula II and III in place of pyridine.

The skilled person would have readily considered replacing pyridine by dimethylaminopyridine (qualitative)

The problem underlying the invention is provision of a further process for the preparation of irinotecan base having surprising effects compared to the closest prior art.

In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the process of the present application having the maximum number of features in common with the prior art process, such that the

invention is shown to have its origins in the distinguishing feature of the invention.

Although the advantage of the claimed process over the prior art processes is indicated in the final paragraph on page 3, it is not considered that it has clearly been demonstrated, in the absence of comparative tests fulfilling the above requirements, that that the claimed process gives rise to a surpring effct compared to the closest prior art.

VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

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Law and Patent Offices
Patents, Trademarks, Designs, Licences

Prague, January 31, 2005

International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva
Switzerland

Re: **International application No. PCT/CZ2004/000050**
Applicant's attitude to Written opinion

Your ref.: PCT/CZ2004/000050
Our ref.: 150381/KB

This is to the Written opinion as mailed by December 3, 2004.

The International Searching Authority (further only as "ISA") assesses the method of the present application (further only as "invention method") as not involving the inventive step taking into account that the substitution of dimethylaminopyridine, as used by the invention method, for pyridine, as used by prior art methods disclosed in the documents D1, D2 and D3, while implementing a condensation of 7-ethyl-10-hydroxycamptothecin with 1-chlorocarbonyl-4--piperidinopiperidine could have been obvious for the skilled person from the above-mentioned three prior art documents.

The Applicant disagrees with the ISA position and promotes his disagreement with the arguments as coming after:

7-Ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin (compound 6-27 according to D1) is prepared in **D1** (left-hand column of page 1451, lines 44-49) as follows: *The solution of 7-ethyl-10-hydroxycamptothecin and chlorocarbonyl diamine (1.1 eq) in* ***pyridine*** *was stirred for 15 h at an ambient temperature. The mixture was evaporated*

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to dryness in vacuo. ***The residue was dissolved in CH_2Cl_2 and the solution was shaken with 7% $NaHCO_3$, the organic layer was dried over $MgSO_4$, filtered and condensed in vacuo. The residue was purified through a silica column with MeOH-$CHCl_3$ (1:20).*** *The final product was obtained in a yield of* ***79,8%*** *as pale yellow powder* (left-hand column of page 1452, line 35).

7-Ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin (compound U-440 according to D2) is prepared in **D2** (column 23, third to fifth complete paragraphs) as follows: ***Pyridine*** *(15 ml) is added to the unpurified 7-ethyl-10-hydroxycaptothecin and the mixture is stirred for 15 minutes at 20° to 25° to dissolve 7-ethyl-10-hydrixycamptothecin. A solution of 4-piperidino--4-piperidinecarbamyl chloride (1,32 g, 5,7 mmole) dissolved in methylene chloride (5 ml) is added. The mixture is stirred at 20-25° for 2 hours to complete the reaction.* ***The mixture is distilled to dryness under reduced pressure. Toluene (20 ml) is added and the mixture is distilled to near dryness under reduced pressure. The unpurified U-440 is dissolved in methylene chloride (25 ml), saturated aqueous sodium bicarbonate solution (5 ml) is added, and the mixture is stirred at room temperature for 5 min. The phases are allowed to settle and the methylenchloride phase is removed. The aqueous phase is extracted with methykene chloride (10 ml). The methylene chloride phases are combined and distilled to yield crude solid U-440. The crude solid U-440 is dissolved in 95:5 methylene chloride-methanol (v/v, 10 ml) and chromatographed on a column packed with 30 g of 230-400 mesh silica, eluting with 95:5 methylene chloride-methanol (v/v). The product containing fractions are combined and distilled to a volume of about 10 ml under atmospheric pressure. Some product crystallization may occur at the end of the distillation. Ethanol (15 ml) is added and the slurry is allowed to stand at -20° C for 24 hours. The product is filtered, washed with ethanol (10 ml), and dried to yield 1,34 g (62% chemical from 16CPT) of U-440.***

7-Ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin is prepared in **D3** (column 25, Example 28)) as

follows: *7-Ethyl-10-hydroxycamptothecin (790 mg, 2,01 mmol) and 1-chlorocarbonyl-4-piperidinopiperidine (910 mg, 3,95 mmole) were dissolved in anhydrous* ***pyridine*** *(50 ml), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was evaporated to dryness in vacuo and* ***the residue was dissolved in $CHCl_3$ (200 ml). The solution was washed successively with 70 aqueous solution of $NaHCO_3$ (200 ml, a saturated aqueous solution NaCl, and the $CHCl_3$ layer was dried with $MgSO_4$, filtered, and evaporated in vacuo. The residual material was decolorized by passing it through a short silica gel column whereby 1,11 g (94,8% in yield) of the title compound was obtained as a pale yellow mass, which was recrystallized from ethanol (ca. 60 ml) to give colorless needles (750 mg, 63,5% in yield).***

It ensues from the foregoing all three methods of D1, D2 and D3, respectively, afford reaction mixtures having to be treated to obtain a pure 7-ethyl-10-[4-(1-piperidino)-1--piperidino]-carbonyloxycamptothecin with very sophisticated treatment processes (these are above bold-faced indicated) which, in turn, considerably decrease the yield of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin. In contrast to this, the invention method provides the reaction mixture that need not be treated so sophisticatedly. The fact is this mixture can be simply worked using only one treatment step to yield the pure 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyl¨-oxycamptothecin, which is washing with acetonitrile (see Example 1 of the present application), as a result of which a yield of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin highly going over 90% is reached. It globally means that if prior art pyridine is replaced with the invention system of a polar aprotic solvent and 4-dimethylaminopyridine while implementing the condensation of 7-ethyl-10-hydroxycamptothecin with 1-chlorocarbonyl-4-piperidinopiperidine a considerably higher yield of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin is obtained which is basic effect of the invention method. This effect could not have been in an obvious way derived by the skilled person from the prior art documents D1-D3 since these documents are absolutely silent on both the mentioned replacement and the higher

yield resulting from this replacement. So, if the skilled person had been acquainted, in the filing time of the present application, with the content of the documents D1-D3 this person could not have found out there any hint motivating to substitute system of the polar aprotic solvent and 4-dimethylaminopyridine for pyridine and thus to come to the invention method. This fact incontestably testifies for that **the invention method does imply the inventive step**. In this regard, the allegation of the ISA that "the skilled person would have readily considered replacing pyridine by dimethylaminopyridine" is to be refused as ill-founded.

The Applicant also disagrees with the allegation of ISA mentioning that the effect of the invention method can not be considered as clearly demonstrated in the present application. The Applicant is, on the contrary, of the opinion that **the effect of the invention method is clearly demonstrated** in the present application by a mere comparison of a prior art yield "about 64%" (see line 6 of page 2 of the present application) with that of the invention method "94,3%" (see Example 1 of the present application). The Applicant takes this yield difference for sufficiently eloquent in favor of the effect of the invention method over that as reached by the prior art methods as objected through the Written opinion.

Concerning the prior art documents D1, D2 and D4 not yet discussed in the present application, the Applicant is prepared to incorporate them into the present application as soon as he is allowed to act so during an imminent proceeding.

On behalf of
PLIVA-Lachema A.S.

Kubát Jan